REMARKS

Reconsideration of the above-identified application in view of the remarks following is respectfully requested. Claims 1-12 are in this case. Claims 1-12 have been rejected. New claims 13-25 have been added.

Objections under 35 USC 132

The Examiner has objected to the amendment as filed on May 27, 2003 under 35 U.S.C. 132 as introducing new matter into the disclosure. The added material teaches a polypeptide having heparanase activity which shares at least 60%, 70%, 80% or 90% homology with SEQ IS NO: 2, and disclosure of the software used to determine this homology.

The Applicant respectfully notes that the parent application (Patent Application Serial No. 08/922,170, now US Patent No. 5,968,822) was incorporated by reference on page 8, lines 2-3 of the present application. The parent application discloses sequence analysis and alignment being performed with the sequence analysis software package developed by the Genetic Computer Group (GCG) at the University of Wisconsin, at page 28, lines 15-19 of the application (corresponding to column 16, lines 17-22 of the granted patent).

Similarly, the parent application discloses (column 6, lines 56-61 of the granted patent), discloses polypeptides having at least 60%, 70%, 80%, 90% homology with SEQ. ID NO: 10 (which is equivalent to SEQ. ID NO: 2 in the instant application, as seen from the sequence listing).

New claims 13-25 have been added to recite an isolated antibody specifically binding to and eliciting at least one epitope of a mammalian heparanase protein, said protein being at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% homologous to SEQ ID NO:2. Support for this is derived from the parent application (now US Patent No. 5,968,822) at column 6, lines 56-61; and column 12, lines 43-48 (corresponding to the granted patent), which teach at least 60, 70, 80 and 90% homology with SEQ ID NO:10. As can be seen from the sequence listing, SEQ ID NO:10 is equivalent to SEQ ID NO: 2 of the instant application.

Rejections over 35 USC 112, first paragraph

The Examiner has rejected claims 1-12 over 35 USC 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. The rejections of the Examiner are respectfully traversed.

The Examiner has generally rejected the claims by stating that there are no teachings of an isolated antibody specifically binding or elicited by at least one epitope of a mammalian heparanase protein, said heparanase protein being at least 80% or at least 90% homologous to SEQ ID NO: 2. The Examiner states that the instant claims encompass antibodies to proteins that are specific for or elicited by heparanases of undisclosed structure, which can be specific for or elicited by any heparanase with at least 80% or 90% homology to SEQ ID NO: 2. According to the Examiner, there is insufficient disclosure in the specification for such antibodies.

Furthermore, the Examiner states that antibodies produced against heparanases having widely disparate amino acid sequences are claimed, with insufficient disclosure of the claimed matter. From the rejections by the Examiner, it seems that the Examiner and Applicant are in agreement that an antibody may be defined in according to the mechanism by which the antibody is elicited, or according to binding characteristics. Binding characteristics are dependant upon recognition of the target peptide structure by the antigen binding site. The claimed antibody of the present invention is characterized by the properties of binding to, or being elicited by, a heparanase protein molecule, which provides a clear characterization of the antibody. Although the structure of the antibody itself cannot be defined in absolute terms, the heparanase epitopes to which it binds, or by which it is elicited, are a clearly identified and essentially homogeneous species, which must exhibit a sufficient level of sequence homology in order to fulfill the structural requirements for recognition by the antibody.

The Examiner states, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass'. This concept of species of biological molecules, (which may include enzymes, antibodies and other proteins, as well as nucleic acid molecules) as

chemical entities is well established in the case law. For example, *THE REGENTS OF THE UNIVERSITY OF CALIFORNIA V ELI LILLY AND COMPANY* (1997, 43 U.S.P.Q.2D (BNA) 1398) described this concept as part of the decision:

> **A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials.**

Although the above passage relates to written description, it is pertinent to Applicant's arguments regarding both enablement and written description because it demonstrates that the court considered DNA molecules to be chemical species as for previously known molecules.

The decision found that the patent in question failed to satisfy the requirements of precise definition, not because DNA molecules are not chemical entities as understood under US patent law, but rather because the patent failed to meet the regular, known standards for such chemical entities:

> **In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.**

Again, there is no question raised that would indicate that DNA molecules are different from any other chemical entities. Indeed, the decision specifically raises the issue of how to describe a DNA genus:

> **A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under § 112, P 1, by showing the enablement of a representative number of species within the genus.**

The decision then continues by quoting the decision in the court case of *In re Angstadt*, 537 F.2d 498, 190 USPQ (BNA) 214 (CCPA 1976) which stated that applicants for a patent "are not required to disclose every species encompassed by their claims even in an unpredictable art". Again, clearly the court looked favorably upon the concept of considering biological molecules as another example of the larger family of chemical entities, deserving of equal consideration as chemical entities.

The Written Description and Enablement requirements of the US Patent and Trademark Office, at least as stated in the rejections by the Examiner, do not appear to take any of the above into consideration. As these requirements are applied by the Examiner, biological molecules become some other type of entities, not molecules at all. Considerations which would not be applied to regular chemistry claims, under the Markush format and Markush practice, somehow become applicable to the present claims.

Homology of biological molecules, including proteins recognized by specific antibodies, and DNA/RNA molecules is an extremely well known tool. Many different databases exist for searching for such sequences according to homology; many different software tools are available for determining such homologies. The value of homology to one of ordinary skill in the art in this field is undoubted, at least to such scientists;

however, the Examiner's rejections clearly ignore these very scientists whose work forms the technology and also provides the determination of "ordinary skill in the art", by imposing requirements that no one of ordinary skill in the art would consider as absolute for determining the value of amino acid sequence homologies.

It is currently not possible to predict with absolute accuracy the function and effect of molecules routinely covered by Markush groups, such as a regular (non-protein or nucleic acid) drug for example, yet broad claim coverage is allowed for entire groups of such molecules on the basis of highly limited examples.

Ex parte Markush, 1925 C.D. 126; 340 O.G. 839 permits claims for molecules to be constructed in the form of a genus expressed as a group of certain specific items (for example functional groups of a backbone; different molecules for composition claims; etc). Markush group claims are used as there is no other way to provide a chemical invention with a suitable scope of claims.

The importance of the Markush concept was to allow the inventor of a new chemical molecule to actually claim related molecules in a clearly defined manner without being required to separately itemize each individual molecule, and also without being required to demonstrate the function or biological efficacy of each individual molecule. Without this concept, even minor changes in a molecule would fall outside the scope of chemical claims, because it would not be possible to list every single molecule in a specification.

In terms of enablement, the Markush concept requires demonstration of the function (such as biological activity) of a small number of examples of the group to be sufficient for supporting enablement for the group. Otherwise, as noted above, a Markush group claim would not be possible. Also as previously described, Markush practice provides that the written description requirement can be fulfilled with a Markush group type recitation and the description of a limited number of examples.

As noted in the case law, even in the "unpredictable art" of chemistry, numerous examples of illustrative molecules are not necessarily required (see description above). Furthermore, written description can stand in for examples of illustrative molecules, also as noted in the case law. However, the Examiner's rejections do not address all of these

important aspects of the Markush concepts and Markush groups, in order to issue sweeping rejections of the present claims for lack of enablement.

Applicant therefore believes that Markush groups are sufficiently well defined for the species of the present invention, in terms of homology of the taught target molecule.

The currently structured claims of the present application deserve the same consideration as though they were written in the form of Markush groups, because in fact a claim structure determined on the basis of homology of amino acid sequence in a target molecule for an antibody is functionally equivalent to a Markush group.

As noted above, a Markush group is a way in which to describe a genus by describing the general parameters or characteristics defining the members of the genus or species. Therefore, the Markush group enables a chemical molecule to be claimed, by defining the parameters required to be a member of that group. These parameters usually include a backbone structure with one or more functional groups, each functional group having a defined set of atoms or moieties comprising a plurality of atoms.

The present claims function in the same manner, as they define the genus (heparanase proteins) according to certain characteristics, namely homology of a defined degree relative to a defined sequence. The defined sequence acts as the equivalent of a chemical "backbone"; the percentage homology acts as the functional groups, as it determines any permissible variations on the backbone structure. All of the above claims relate to a specific stated sequence. All of the above claims relate to homology of a defined percentage, the lowest percentage being 60%. Certain of the claims provide specific guidance on how to determine the percentage of homology in a very specific manner, including the software to be used and parameters for that software, if in fact such specific guidance is even necessary.

As the present claims clearly follow Markush practice, they are deserving of the same consideration as Markush practice for any other molecule or chemical entity, as described above.

These points now lead to consideration of the next issue, the factors determined according to *In re Wands*. According to the rejections of the Examiner, undue

experimentation is involved with regard to the present claims, as the specification does not provide sufficient support for the scope of the claims. Applicant wishes to traverse by examining each of the *Wands* factors with regard to the present claims as follows:

Wands factor 1:

Undue experimentation is related to the quantity of experimentation necessary. By "quantity of experimentation" it is clearly meant experimental effort and experimental work. *Wands* itself states that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed".

The present application actually provides a simple, routine test in order to determine whether a particular protein sequence belongs to the claimed invention. First, selecting a sequence as being homologous (according to a defined percentage of homology) to the sequence stated in the claim is trivial. The present application also provides specific guidance on how to determine homology, including naming a suitable software tool and suitable conditions for operating the tool.

Second, clearly preparing the protein itself from a sequence corresponding to the present claims would be simple, as preparing a vector for a protein of a known sequence, and inserting that vector into a suitable cell line, are both clearly well defined activities for which many commercial kits and tools are available. Applicant notes that the present application gives further support by noting the suitability of an insect cell line and guidance with regard to the choice of cell line. Thus, the protein could be readily prepared.

Once prepared, the function of the protein could easily be tested as part three, since the present application provides a simple assay for testing heparanase activity. This assay is on the level of a Western blot or any other routine research tool in its simplicity and ease of use.

These three steps are all that is required to test whether a particular protein sequence falls within the present claims:

1. select a sequence according to homology (trivial)

2. produce the protein having that sequence (routine)

3. test the protein for heparanase function (routine)

Thus, the amount of experimentation required is not undue in terms of quantity with regard to the statements in *Wands* itself.

Wands factor 2:

The amount of direction or guidance presented (in the specification). As noted above, the present application provides a great deal of direction and guidance as exactly how to select a protein having heparanase activity and also having the required sequence homology. Since all of the steps of the test are either routine or trivial, no further direction or guidance is required.

Wands factor 3:

The presence or absence of working examples. The present application also provides working examples which are sufficient to demonstrate the claimed invention, particularly given the state of the technological art. After all, there can be no argument that the claimed sequences are protein sequences (or in a few cases protein sequences determined according to nucleotide sequences), nor (since it is specified in the claims) that only those protein sequences producing proteins having heparanase activity are included. The only question raised by the Examiner is whether the resultant proteins have heparanase activity. Since Applicant described a simple test above for determining such activity, and since the working examples are more than sufficient to describe all of the above aspects of the invention, there are clearly enough working examples.

Wands factor 4:

The nature of the invention. The exact nature of the invention is clear as noted above: proteins having heparanase activity, being determined according to a sequence (with regard to defined homology). Protein sequences have actually become one among many tools for exploring biological function, providing new medicines, and so forth. Proteins themselves are complex chemical entities, but they are still chemical entities,

regardless of their complexity (they are actually a type of polymer, which are recognized chemical entities). They should accorded their fair status as a type of chemical entity.

Wands factor 5:

The state of the prior art. This requirement does not seem to be addressed by the rejections of the Examiner. As noted in the present application, routine "cookbooks" for molecular biology existed at the time of filing. Assuming that a protein sequence was known, the gene for the protein could be readily cloned and recombinant protein easily produced. In those cases, such as heparanase, where discovering the sequence was difficult and the initial cloning and production of recombinant protein was also difficult, once the sequence and a suitable method for production were discovered, again recombinant protein could easily be produced: see for example **Shelton DL et al.** J Neurosci. 1995 Jan;15(1 Pt 2):477-91; **Hays WS,** Biochem J. 1996 Nov 1;319 (Pt 3):829-37; **Kitzler JW** Prostaglandins Leukot Essent Fatty Acids. 1996 Oct;55(4):269-77. The test for heparanase activity described in the present application was certainly only a variation on a routine test, given that the art (such as Fuks) cited by the Examiner also includes such a test.

Wands factor 6:

The relative skill of those in the art. Here there can be no doubt; the relative skill of those in this technological art has been recognized in many court decisions as being quite high, as one of ordinary skill in the art could easily be a team of PhD level scientists. For such individuals, the above tests would be easy and routine to perform.

Wands factor 7:

The predictability or unpredictability of the art. Molecular biology is an unpredictable art, as is chemistry. Applicant does not dispute this fact, but rather questions the apparent assumption in the rejections of the Examiner that molecular biology is somehow *more unpredictable* than chemistry. If anything, molecular biology (or at least the sub-field relating to protein and DNA/RNA sequences) should be *less unpredictable* than the wider field of chemistry. After all, a protein sequence is readily

identifiable as such; it will result in a protein and not some other type of chemical. Other non-protein chemical structures are not nearly so clear with regard to the classification of the resultant chemical. Thus, Applicant feels that protein and DNA/RNA sequences should be considered with the same level of unpredictability as regular chemicals, for these reasons and also for the reasons given above.

Wands factor 8:

The breadth of the claims. The breadth of Applicant's claims is actually not overly broad, given that all of the claims are now somehow related to a particular protein sequence. Applicant does not seek to claim every "heparanase", but only those proteins having defined homology to the claimed sequence. Thus, Applicant's claims are actually quite focused.

Applicant respectfully maintains that a clear structural relationship is drawn between the species disclosed in the specification and the claimed antibody, given the recitation of the binding of heparanase protein by the antibody. In addition, a clear relationship is drawn between the function of the claimed antibody and that of the disclosed species. The relationship is evident due to both the functional similarity of the species and the high degree of homology.

It is well known in the art that amino acid sequences in the constant portion of the heavy chain of an antibody are characteristic of a given isotype, which differs between species, and that each antibody isotype has unique structural features that imparts specialized biological functions. Comparison of the heavy chains within subclasses of a given antibody class generally reveals greater than 80-90% homology in the constant regions of the heavy chain.

With regard to heparanase, a certain degree of cross-reactivity has been shown to exist between isotypes of different species, as testified in the attached affidavit, indicating a strong similarity between the structure of the antibody of different species.

The interspecies sequence homology is reflected in the three-dimensional configuration, conferring both immunological and functional similarity across species.

Heparanases purified from different human and animal sources share similar substrate specificities, yield similar oligosaccharide cleavage products and are inhibited by heparin substrate derivatives.

Polyclonal and monoclonal heparansae antibodies recognize mouse heparanase, chick heparanase, the human platelet heparanases, and the heparanase enzymes produced by several human tumor cell lines and recombinant human heparanase expressed in Chinese hamster ovary (CHO) cells. By virtue of their specificity, these antibodies are highly appropriate for treatment of heparanase-related and other medical conditions, and for diagnostic purposes such as immunohistochemistry of biopsy specimens and quantitative ELISA of body fluids (e.g., plasma, urine, pleural effusions, etc.).

This immunological cross-reactivity, along with the conservation of functional sites, indicates that anti-heparanase antibodies of the present invention can effectively bind to and neutralize a wide range of heparanase enzymes from diverse species having specified levels of overall sequence homology.

The amino acid sequence of the target binding site is not of major significance per se, since the antibodies does not recognize linear chains, but three-dimensional structures. The important factor is therefore the manner in which variations in such a sequence affect the structure of the binding site as recognized by the antibody. As stated in the previous response, Applicant notes that the present Application clearly teaches an assay for heparanase activity, as described on p. 40, line 21 to the end, bridging to p. 41, lines 1-13. Such an assay could easily be used by one of ordinary skill in the art to determine which proteins having a sequence that falls within the definition of 60, 70, 80 or 90% homology in the claims also have heparanase activity.

It is also irrelevant where the heparanase binding sites are situated, as recognition by the antibody is not dependant upon the position of the site with regard to the protein sequence.

Thus, in summary, Applicant feels that the following issues have been clearly determined against the rejections of the Examiner:

1. Regarding written description, Applicant has provided a protein sequence, a defined percentage of homology from that sequence, a software tool and parameters for determining homology, and an assay for determining heparanase activity. The present claims also clearly define a genus in terms of the required parameters or characteristics of species belonging to the genus, as required by Markush practice. Thus, the present application is enabled for written description.

2. Regarding enablement, the above showings clearly also demonstrate that the claimed invention is sufficiently described in the specification so as to allow one of ordinary skill in the art to make or use (practice) the invention without undue experimentation.

3. All of these findings are commensurate with the view of DNA/RNA molecules and proteins as being chemical entities and therefore as being subject to the same requirements as chemical entities.

In view of the above remarks, Applicant considers that the present claims are clearly supported and described by the specification, since a clearly homologous species of antibody is taught, defined in terms of the homology of the target binding site which it recognizes for selective binding. The claims teach minimum levels of amino acid sequence homology required for binding of this antibody to be effected, or for the antibody to be elicited.

In view of the above amendments and remarks, it is respectfully submitted that Claims 1-25 are in condition for allowance. An early Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,

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